Specification

A novel triazole derivative.

The Field of the Technology

This invention relates to a drug, in particular a novel triazole derivative or pharmacologically acceptable salt thereof and a V_{1A} receptor antagonist of arginine vasopressin containing these as an active component.

Background technique

Diabetic nephropathy is one of three major complication of diabetes mellitus, and signs such as trace albuminuria, albuminuria, renal function disorder, hypertension, edema and the like are observed clinically, and in many cases renal failure is finally caused. This diabetic nephropathy progresses comparatively slowly in the early stages, and lesions thereof are said to be reversible, however, at dominant period when albuminuria becomes positive, the lesions become irreversible, and a rapid lowering of renal function is caused which leads to terminal stage renal failure. Presently, the pathology can be diagnosed before the albuminuria becomes positive by measurement of trace albuminuria and the like, and as a measure for the prevention of nephropathy progress, it is thought that positive therapy should be carried out in the early stages at which the lesion is reversible.

It is reported that arginine vasopressin (hereinafter it is described as AVP) concentration in plasma is increased in diabetic patient and diabetes mellitus model animal (Diabetes, 38 [1989], 54-57), moreover, as physiological action of AVP in kidney through V_{1A} receptor, a direct contraction action of efferent arteriole (Am. J. Physiol, 256 [1989], F274-F278) and an increase of kidney glomerulus internal pressure due to dilation of afferent arteriole via synthetic facilitation action of prostaglandin E2 species (J. Hypertens. 11 (1993), 127-134), kidney mesangial cell proliferation, hypertrophy and extracellular matrix accumulation (Am, J. Physiol. [1988], F898-F906) have been elucidated, and a close link to onset and progression of pathology of diabetic nephropathy has been suggested. Moreover, there is a clinical report that OPC-21268 which is V_{1A} receptor selective antagonist (compound of Example 141 in EP 382185 bulletin) improves albuminuria in NIDDM patient in practice (Arzneim. Forsch. 46 [1996], 875-878). Accordingly, V_{1A} receptor antagonists are expected to be an effective prevention and treatment agent for diabetic nephropathy.

Moreover, recently it has become clear that AVP strongly promoted production of vascular permeability facilitation factor (other name, vascular endothelium growth factor) through V_{1A} receptor

expressed on vascular smooth muscle (Eur. J. Pharmacol. 368 [1999], 89-94), therefore, a link to formation process of blood vessel lesion in various kinds of diseases such as diabetic retinopathy and nephropathy, arteriosclerosis or the like, is indicated (Biochimica et Biophysica Acta 1243 [1995], 195-202). Accordingly the V_{1A} receptor antagonist is useful for prevention and treatment of blood vessel diseases in various kinds of diseases.

On the other hand, V_2 receptor antagonist is known to have water diuretic action, and compound having antagonism activity with respect to both V_{1A} and V_2 receptors is preferred for renal disease accompanied by edema, and for example benzazepine derivatives described in WO95/03305 and WO95/06035 are known as such compounds. However, selective V_{1A} receptor antagonists are considered to be more preferable in diseases that are not accompanied by edema, for example, diabetic nephropathy having symptoms such as mouth dryness, polyuria or the like.

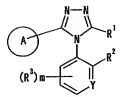
Moreover, oxytocin is known as the peptide hormone having highly analogous amino acid sequence to AVP and it is made biosynthesised in hypothalamus-pituitary gland system in the same way, and it is known that a certain type of AVP receptor antagonist also antagonises this oxytocin receptor and causes inhibition with respect to physiological effect such as uterine contraction, milk discharge or the like.

Accordingly it is anticipated that the compound which is V_{1A} receptor selective with respect to V_2 receptor and oxytocin receptor and also has stronger antagonism activity will be a suitable therapeutic agent for the disease that is not accompanied with edema such as diabetic nephropathy or vascular disease in various kinds of diseases or the like.

Under above-mentioned background, these inventors carried out screening of a compound which is selective and has high V_{1A} receptor affinity, as a result discovered that one species of specific triazole derivative satisfied aforesaid condition. This invention was completed as a result of this.

Disclosure of the invention.

This invention is a medicinal composition characterised in containing a triazole derivative represented by following general formula (I) or a pharmacologically acceptable salt thereof and a pharmacologically acceptable carrier, and in particular it relates to vasopressin V_{1A} receptor antagonist.



(I)

(wherein, the symbols in the formula have the following definitions,

A ring:

a) a benzene ring which may be substituted by 1-3 substituents selected from halogen, nitro, amino, lower alkyl group or a group represented by -X-R4 or,

b) a thiophene ring which may be substituted by aryl group,

R1: hydrogen atom or lower alkyl group,

R2: hydrogen atom, halogen atom, hydroxyl group, optionally substituted alkoxy group, optionally substituted lower alkyl group, optionally substituted lower alkynyl group or optionally substituted amino group,

R3: hydrogen atom, halogen atom, amino, nitro, cyano, trifluoromethyl, lower alkyl, -O-lower alkyl group, or

it may link with R2 group to form a cycloalkyl ring,

Y: CH or N,

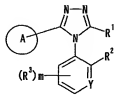
X: single bond, -NH-CO-, -CO-NH-, -NH-CO-NH-, -NH-CS-NH-, -(CH2)k-O- or -O-(CH2)k- group,

R4: an aryl group which may be substituted by lower alkyl or aryl group; a 5-6 membered heteroaryl group which may be substituted by lower alkyl group; a 3-8 membered saturated heterocyclic group which may be substituted by lower alkyl group,

m: an integer of 1-3,

k: an integer of 0-5).

Moreover this invention relates to a triazole derivative represented by following general formula (I')



(I')

(wherein, the symbols in the formula have the following definitions,

A ring:

a) a benzene ring which may be substituted by 1-3 substituents selected from halogen, nitro, amino, lower alkyl group or a group represented by -X-R4 or,

b) a thiophene ring which may be substituted by aryl group,

R1: hydrogen atom or lower alkyl group,

R2: hydrogen atom, halogen atom, hydroxyl group, optionally substituted alkoxy group, optionally substituted lower alkyl group, optionally substituted lower alkynyl group or optionally substituted amino group,

R3: hydrogen atom, halogen atom, amino, nitro, cyano, trifluoromethyl, lower alkyl, -O-lower alkyl group, or

it may link with R2 group to form a cycloalkyl ring,

Y: CH or N,

X: single bond, -NH-CO-, -CO-NH-, -NH-CO-NH-, -NH-CS-NH-, -(CH2)k-O- or -O-(CH2)k- group,

R4: an aryl group which may be substituted by lower alkyl or aryl group; a 5-6 membered heteroaryl group which may be substituted by lower alkyl group; a 3-8 membered saturated heterocyclic group which may be substituted by lower alkyl group,

m: an integer of 1-3,

k: an integer of 0-5,

Wherein, the compound wherein A ring is biphenyl group, R1 group is methyl group, Y is CH, m is 1, R3 group is hydrogen atom, and also R2 group is methoxy group is excluded), or a pharmacologically acceptable salt thereof.

Triazole derivatives in accordance with this invention are explained further.

A preferred compound of this invention is a triazole derivative wherein in aforesaid general formula (I) and (I'),

R2 group is

1) an alkoxy, lower alkyl or lower alkynyl group having substituent selected from the group represented by formula -R5, -O-(CH2)p-R5, -NH-(CH2)p-R5, -CO-(CH2)p-R5, -CO-O-(CH2)p-R5 and -CO-NH-(CH2)p-R5;

[wherein, R5 is i) hydrogen atom, or ii) aryl, a 5-6 membered heteroaryl or a 3-8 membered saturated heterocyclic group (these ring groups may be further substituted by halogen atom, amino, nitro, cyano, lower alkyl, -O-lower alkyl, -COO-lower alkyl, -CO-3-8 membered saturated heterocycle, -CO-3-8 membered saturated heterocycle-3-8 membered saturated heterocycle, -CO-3-8 membered saturated heterocycle-lower alkyl, aryl, a 5-6 membered heteroaryl or a 3-8 membered saturated heterocyclic group which may be substituted by lower alkyl group), and p is an integer of 0-4]; or

2) a group represented by

(wherein X is CH-R6, N-R6, O or S, R6 is lower alkyl, -O-lower alkyl, -COO-lower alkyl, -CO-3-8 membered saturated heterocycle-lower alkyl, aryl, a 5-6 membered heteroaryl or a 3-8 membered saturated heterocyclic group, and q, r are integers of 1-3);
or a pharmacologically acceptable salt thereof,
moreover, a triazole derivative wherein
A ring is a group represented by formula

(wherein, X and R4 are as described before, and R7 is hydrogen atom, halogen atom, nitro, amino or lower alkyl group).
or a pharmacologically acceptable salt thereof.

A further preferred compound in this invention is a triazole derivative wherein Y is CH and R2 group is a group selected from the group represented by following formula or a pharmacologically acceptable salt thereof.

-O-(CH2)n-R5
-O-(CH2)n-O-(CH2)p-R5
-O-(CH2)n-NH-(CH2)p-R5
-O-(CH2)n-CO-(CH2)p-R5
-O-(CH2)n-CO-O-(CH2)p-R5
-O-(CH2)n-CO-NH-(CH2)p-R5
(wherein, R5 and p are described as above, and n is an integer of 1-12).

The most preferred compound in this invention is a triazole derivative wherein the A ring is 4-biphenyl ring, R1 is methyl group and R2 is a group represented by -O-(CH2)n-R5, or a pharmacologically acceptable salt thereof, and as embodiments the following compounds are nominated.
8.(sic) 4-(2-benzyloxyphenyl)-3-(4'-biphenyl)-5-methyl-1,2,4-triazole,
4-{2-[5-(4-methylpiperazin-1-yl) pentyloxy] phenyl}-3-(4'-biphenyl)-5-methyl-1,2,4-triazole,
4-{2-[6-(4-methylpiperazin-1-yl) hexyloxy] phenyl}-3-(4'-biphenyl)-5-methyl-1,2,4-triazole,

4-{2-[7-(4-methylpiperazin-1-yl) heptyloxy] phenyl}-3-(4'-biphenyl)-5-methyl-1,2,4-triazole,
4-{2-[8-(4-methylpiperazin-1-yl) octyloxy] phenyl}-3-(4'-biphenyl)-5-methyl-1,2,4-triazole,
4-{2-[6-(4-methylpiperazine-1-yl) hexyloxy]-6-methylphenyl}-3-(4'-biphenyl)-5-methyl-1,2,4-triazole,
4-{2-[6-(4-methyl homopiperazin-1-yl) hexyloxy]-6-methylphenyl}-3(4'-biphenyl)-5-methyl-1,2,4-triazole,
4-[2-(6-piperidino hexyloxy) phenyl]-3-(4'-biphenyl)-5-methyl-1,2,4-triazole,
4-{2-[6-(4-piperidino piperidin-1-yl) hexyloxy] phenyl}-3-(4'-biphenyl)-5-methyl-1,2,4-triazole,
4-{2-[6-(4-piperidino piperidin-1-yl) hexyloxy]-6-methylphenyl}-3-(4'-biphenyl)-5-methyl-1,2,4-triazole,
4-{2-[4-(4-piperidyl) butoxy] phenyl}-3-(4'-biphenyl)-5-methyl-1,2,4-triazole,
4-{2-[4-(4-methylpiperazin-1-yl) carbonyl phenyl] methoxy-6-methylphenyl}-3-(4'-biphenyl)-5-methyl-1,2,4-triazole,
4-{2-[4-(4-piperidino piperidin-1-yl) carbonyl phenyl] methoxy-6-methylphenyl}-3-(4'-biphenyl)-5-methyl-1,2,4-triazole,
4-{2-[4-(4-methylpiperazin-1-yl) carbonyl phenyl] methoxyphenyl}-3-(4'-biphenyl)-5-methyl-1,2,4-triazole or
4-{2-[3-(3-pyridyl) propyl] phenyl}-3-(4'-biphenyl)-5-methyl-1,2,4-triazole.

Moreover, the "lower" in the definition of group of general formula of this specification means a straight or branched chain carbon chain having carbon number of 1-6 unless otherwise stated in particular.

Accordingly, the "lower alkyl group" is a 1-6C alkyl group and for example it is methyl, ethyl, propyl, butyl, pentyl, hexyl group or structural isomer of these such as isopropyl group and the like, preferably 1-4C alkyl group and more preferably methyl or ethyl group.

The "lower alkynyl group" is 2-6C alkynyl group, and for example it is ethynyl group, 1-propynyl group, 1-butynyl group, 1-pentynyl group, 1-hexynyl group or a constitutional isomer of these such as 1-methyl-2-propynyl group and the like, and preferably ethenyl group.

Moreover, the "alkoxyl group" is 1-12C alkoxyl group and example includes methoxy group, ethoxy group, propoxy group, butoxy group, pentyloxy group, hexyloxy group, heptanoxy group, octanoxy group, nonanoxy group, decanoxy group, undecanoxy group, dodecanoxy group or a branched alkoxyl group containing the same carbon number as these.

As "halogen atom", fluorine atom, chlorine atom, bromine atom, iodine atom are nominated.

The "aryl" is 6-14C aromatic ring which may have substituent, and for example, benzene, naphthalene, anthracene, phenanthrene group and the like are proposed, and benzene is preferred.

The "5-6 membered heteroaryl" is a 5 or 6 membered aromatic ring containing 1-4 N, O or S atoms, which may have substituent, and for example, furan, pyrrole, thiophene, imidazole, pyrazole, oxazole, thiazole, triazole, pyridine, pyrazine, pyrimidine, tetrazole and the like are nominated.

The "3-8 membered saturated heterocycle" is a 3-8 membered saturated monocycle containing 1-3 N atoms which may contain O or S atom, and for example, azepin, pyrrolidine, piperidine, piperazine, morpholine and the like are nominated.

As substituent of "optionally substituted alkoxyl group", "optionally substituted alkyl group" and "optionally substituted alkynyl group" of R2 group, an aryl, a 5-6 membered heteroaryl or a 3-8 membered saturated heterocyclic group or a group wherein these ring groups are substituted through -O-(CH2)p-, -NH-(CH2)p-, -CO-(CH2)p, -CO-O-(CH2)p, -CO-NH-(CH2)p- groups (p is an integer of 0-4), or otherwise halogen atom, amino, cyano, nitro,-OH, -O-lower alkyl, -NH-lower alkyl, -N-di lower alkyl, -CO-lower alkyl, -COOH, -COO-lower alkyl, -CONH2, -CONH-lower alkyl group are nominated. Wherein, the aryl, 5-6 membered heteroaryl and 3-8 membered saturated heterocyclic group may further contain substituent. The substituent of these ring groups can be any of substituent which is usually used, and for example, a lower alkyl (said lower alkyl may be substituted by 1-4 substituents selected from the group comprising halogen atom, -O-lower alkyl, -COOH, amino, -NH-lower alkyl and N-di-lower alkyl group), a halogen atom, amino, nitro, cyano, -OH, -O-lower alkyl, -COOH, -COO-lower alkyl, -CO-3-8 membered saturated heterocycle, -CO-3-8 membered saturated heterocycle-3-8 membered saturated heterocycle, -CO-3-8 membered saturated heterocycle-lower alkyl, -NH-lower alkyl, -N-di lower alkyl, -S-lower alkyl, -SO-lower alkyl, -SO2-lower alkyl, -CONH2 , -CONH-lower alkyl, aryl, 5-6 membered heteroaryl or a 3-8 membered saturated heterocyclic group which may be substituted by lower alkyl group are proposed, and these may have 1-3 substituents.

Preferred species of substituent of "optionally substituted alkoxyl group", "optionally substituted alkyl group" and "optionally substituted alkynyl group" comprises a group represented by formula -R5, -O-(CH2)p-R5, -NH-(CH2)p-R5, -CO-(CH2)p-R5, -CO-O-(CH2)p-R5 or -CO-NH-(CH2)p-R5 (wherein,

R5 is i) hydrogen atom, or ii) aryl, a 5-6 membered heteroaryl or a 3-8 membered saturated heterocyclic group (these ring groups may be further substituted by halogen atom, amino, nitro, cyano, lower alkyl, -O-lower alkyl, -COO-lower alkyl, -CO-3-8 membered saturated heterocycle, -CO-3-8 membered saturated heterocycle-3-8 membered saturated heterocycle, -CO-3-8 membered saturated heterocycle-lower alkyl, aryl, a 5-6 membered heteroaryl or a 3-8 membered saturated heterocycle which may be substituted by lower alkyl group), and p is an integer of 0-4).

As example of such "optionally substituted alkoxyl group", the following species are nominated. Phenylalkoxy group, (4-alkylpiperazin-1-ylcarbonyl) phenylalkoxy group, (4-piperidinopiperidino carbonyl) phenylalkoxy group, (piperidinocarbonyl), phenylalkoxy group, (4-alkylpiperazin-1-ylcarbonyl) alkoxy group, (4-piperidino piperidinocarbonyl) alkoxy group, (piperidinocarbonyl) alkoxy group, (morpholinocarbonyl) alkoxy group, (alkoxycarbonyl) alkoxy group, (hydroxycarbonyl) alkoxy group, [(4-alkyl piperazin-1-yl) alkylamino carbonyl] alkoxy group, [4-(pyrimidin-2-yl) piperazin-1-yl] alkoxy group, [4-(2-pyridyl) piperazin-1-yl] alkoxy group, (4-alkyl piperazin-1-yl) alkoxy group, (4-alkyl homo piperazin-1-yl) alkoxy group, (4-piperidino piperidino) alkoxy group, [(piperidinyl-1-yl) alkylamino] alkoxy group, piperidinoalkoxy group, piperidylalkoxy group, morpholinoalkoxy group, pyridylalkoxy group, imidazolylalkoxy group, (2-aminophenoxy) alkoxy group, hydroxyalkoxy group, and the like are nominated.

The "optionally substituted amino group" of R2 group may even be an amino group substituted by lower alkyl group, moreover a saturated heterocycle including N atom may be formed together with substituent. Preferably, it is a group represented by formula

.

Wherein, X is CH-R6, N-R6, O or S, R6 is lower alkyl, lower alkyl-O-, lower alkyl-O-CO-, lower alkyl-3-8 membered saturated heterocycle-CO-, aryl, a 5-6 membered heteroaryl or a 3-8 membered saturated heterocyclic group, and q, r are integers of 1-3.

As cycloalkyl formed by linking R2 group and R3 group, for example, cyclobutyl group, cyclopentyl group, cyclohexyl group, cycloheptyl group, cyclo octyl group and the like are nominated.

The following is nominated, as example wherein the A ring is a phenyl group substituted by group represented by -X-R4.

Phenoxyphenyl group, phenylalkoxyphenyl group, (2-biphenyl) carbonylaminophenyl group, biphenyl group which may be substituted by lower alkyl group, furylcarbonylaminophenyl group which may be substituted by lower alkyl group, biphenyl group, piperidino phenyl group, (piperidino alkoxy) phenyl group, optionally substituted pyrrolidinyl phenyl group, optionally substituted imidazolyl phenyl group, optionally substituted thiazolyl phenyl group, morpholino phenyl group, (morpholino alkoxy) phenyl group, phenylureinphenyl group which may be substituted by lower alkyl group, phenylthioureinphenyl group which may be substituted by lower alkyl group, phenoxyphenyl group, phenylthiophenyl group and the like are nominated.

There is the case that the compounds of this invention can form a salt with inorganic acid or organic acid, and salts thereof also have V1 action inhibitory action. As suitable salt, for example, salt of mineral acid such as or hydrochloric acid, hydrobromic acid, hydroiodic acid, sulphuric acid, nitric acid, phosphoric acid or the like, salt of organic acid such as formic acid, acetic acid, propionic acid, oxalic acid, malonic acid, succinic acid, fumaric acid, maleic acid, lactic acid, malic acid, tartaric acid, citric acid, carbonic acid, glutamic acid, aspartic acid, methanesulfonic acid, ethanesulfonic acid or the like, salt of inorganic base such as sodium, potassium, magnesium, calcium, aluminium and the like, salt of organic base such as methylamine, ethylamine, ethanolamine and the like, salt of basic amino acid such as lysine, ornithine and the like are nominated. Moreover, a quaternary ammonium salt can be formed by reaction with lower alkyl halide, lower alkyl triflate, lower alkyl tosylate or benzyl halide and the like, but, salts with methyl iodide, benzyl chloride and the like are preferred as quaternary ammonium salt.

In the compounds of this invention, optical isomers on the basis of asymmetric carbon atom and geometric isomers on the basis of double bond and cyclohexane ring may be present, and when two or more asymmetric carbon atoms are contained, furthermore, diastereoisomers are present. The isolated species and mixture of isomers of these various isomers are included in this invention. Moreover, hydrate, various solventate and tautomer and the like are included in the compounds of this invention. Moreover, the compounds of this invention also include compounds having crystal polymorphism, and those crystal forms are all included in the compounds of this invention.

The compounds which are the effective ingredient of drug in accordance with this invention are novel compounds except for a compound wherein in general formula (I), A ring group is 4-biphenyl group, R1 group is methyl group, Y is CH, m is 1, R3 group is hydrogen atom and also R2 group is methoxy

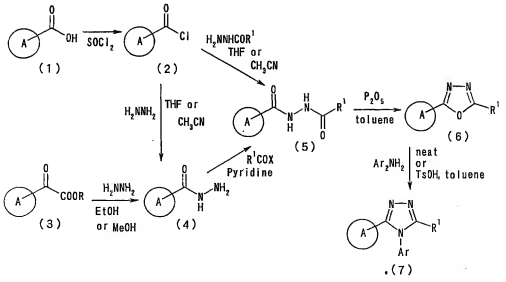
group. A compound wherein in aforesaid formula (I), A ring group is 4-biphenyl group, R1 group is methyl group, Y is CH, m is 1, R3 group is hydrogen atom and also R2 group is methoxy group was synthesised by Labotest Co. (Freiburg, Germany) and this is obtainable from Labotest Co. by request.

(Process for the production)

A process for the production of compound in accordance with this invention is explained.

3,4-diaryl substituted-5-substituted-1,2,4-triazole derivative (7) which is the basic skeleton can be produced usually using two processes shown below.

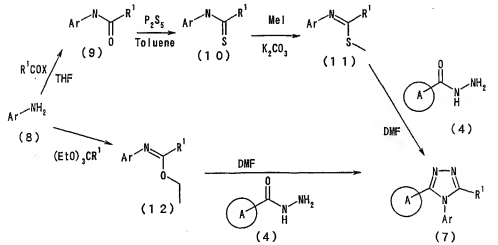
First of all, as the first process, an aromatic carboxylic acid (1) is activated as aromatic carboxylic acid chloride with thionyl chloride and the like and is condensed in an inert solvent such as tetrahydrofuran and acetonitrile and the like as shown in equation below, or an acid hydrazide (4) obtained by reacting an aromatic carboxylic acid ester with 10 equivalents of hydrazine in an alcohol, is condensed in the presence of acylating agent such as acetic anhydride and organic base such as pyridine, or an aromatic carboxylic acid chloride (2) is reacted directly with acid hydrazide and thereby a diacyl hydrazine (5) is obtained, the diacyl hydrazine (5) obtained in this way is cyclised in the presence of dehydrating agent such as phosphorus pentoxide, and thereby 1,3,4-oxazole (6) is obtained. This is heated with anilines in the absence of solvent, or heated under reflux in a solvent such as toluene in the presence of acid catalyst such as tosyl acid or the like, and thereby the target 1,2,4-triazole derivative (7) can be obtained.



Moreover, a process for the production of 1,3,4-oxadiazole (6) is described in E. Klinsberg, J. Am. Chem. Soc., 1958, 80, 5786-5789, which can be referred to in accordance with requirements.

Moreover, as the acid catalyst used during heating under reflux, mesyl acid, camphor sulphonic acid and the like can be used besides tosyl acid, and xylene, mono- or di-chlorobenzene and the like can be used besides toluene as solvent.

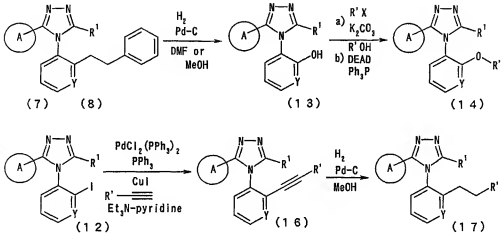
As the second process, an aniline derivative (8) is condensed with acylating agent such as acetic anhydride in an organic solvent such as tetrahydrofuran and the like, thereby an anilide (9) is obtained, this is thioamidated using phosphorus pentasulfide in an organic solvent such as toluene and the like, thereby a thioamide (10) is obtained, the thioamide (10) obtained in this way is formed into S-methylthio imidate (11) with methyl iodide, this is reacted with acid hydrazide (4) in dimethyl formaldehyde (hereinafter, abbreviated to DMF) by heating to 120°C, and thereby a 1,2,4-triazole derivative (7) is obtained. Or, a compound (8) is heated with ortho acid ester, thereby O-alkyl imidate (12) is formed, this is reacted with acid hydrazide (4) in the same way as above, and a 1,2,4-triazole derivative (7) can be obtained. In the reaction with acid hydrazide (4), dimethylacetamide, DMSO, 1-methyl-2-pyrrolidone and the like can be ideally used besides DMF as solvent.



Conversion process of side chain such as R2 group or the like is explained next.

As conversion process of side chain, the following process is nominated. In other words, a benzyloxy derivative (7) is debenzylated by catalytic reduction, thereby a phenol derivative compound (13) is obtained, and an alkyl group is introduced to this by Mitsunobu's reaction with an alkyl halide, an alkyl sulphonate or an alcohol, and thereby an alkyloxyphenyl triazole derivative (14) is obtained.

Moreover, an alkylene dihalide and a phenol derivative compound (13) are reacted, thereby a halogeno alkyloxyphenyl triazole derivative is formed, this is subjected to substitution reaction with an amine, and thereby an aminoalkoxy phenyl triazole derivative is obtained. Moreover, an iodine body (15) is subjected to Sonogashira reaction (PdCl2 (PPh3)2, CuI, PPh3, acetylene/Et3N-pyridine), thereby an alkylene derivative (16) is obtained, this is catalytically-reduced, and thereby an alkylphenyl triazole derivative (17) is obtained.



Moreover, in the compounds of this invention, a racemic body, isomers such as optically active body, diastereomer and the like may be present as single species or a mixture thereof as described above. A racemic compound can be derived to a stereochemically pure isomer using a suitable starting material compound, or by general racemic resolution method (for example, an optical resolution method by deriving to a diastereomeric salt with general optically active acid (tartaric acid and the like)). Moreover, the mixture of diastereomers can be separated by conventional method, for example fractional crystallisation or chromatography and the like.

Possible applications in industry

The compounds of this invention have selective antagonism activity to V_{1A} receptor compared with V_2 receptor of AVP and oxytocin receptor, and for example have vasodilation action, hypotensive action, cardiac function facilitating action, myocardial cell hypertrophy inhibitory action, vascular smooth muscle cell contraction / proliferation / hypertrophy inhibitory action, kidney mesangial cell contraction / proliferation / hypertrophy inhibitory action, kidney extracellular matrix accumulation inhibitory action, platelet agglutination inhibitory action, vascular permeability factor (vascular endothelium proliferator) production inhibitory action.

Moreover, because the action of the compounds of this invention on AVP receptor is V_{1A} receptor selective, it can be used for therapy of diseases involving V_{1A} receptors of AVP without accompanying actions such as water diuretic action on the basis of V_2 receptor antagonism or uterine contraction or the like on the basis of oxytocin receptor antagonism, and it is useful as for example vasodilator, antihypertensive drug, anti-cardiac failure drug, anti renal failure drug, antiplatelet agglutination depressant and it is effective for prevention and therapy of for example hypertension, cardiac failure, renal disease, cerebral blood vessel disorder, diabetes mellitus, diabetic nephropathy, diabetic retinopathy, various ischemic disease, circulation incompetence, arteriosclerosis, dysmenorrhea, gastric ulcer, nausea, vomition, syncope, malignant tumour, cancer, renal function disorder or the like. It is useful in particular, for prevention and treatment of diabetic nephropathy.

The compounds of this invention have excellent oral absorption ability and are not readily metabolised in vivo, and have excellent prolonged action.

Below, the pharmacological action of the compounds of this invention is described by Test Examples.

(1) Receptor binding examination using human V_{1A} receptor expression cell membrane sample.
The production of human V_{1A} receptor expression cell was performed in accordance with process of Thibonnier et al. (J. Biol. Chem. 269 [1994], 3304-3310). [^{3}H]AVP(0.5 nM) and human V_{1A} receptor expression cell membrane sample were mixed with test drug agent of various concentration and incubated. The assay was carried out using assay buffer of 50 mM Tris-hydrochloric acid buffer (pH = 7.4) including 10 mM magnesium chloride, 0.1 % bovine serum albumin with whole quantity of 250 µl with the incubation time of one hour at 25°C. On completion of the incubation, filtration under reduced pressure was carried out using cell harvester, the sample was passed through a glass filter (GF/B), thereby free ligand and excess buffer were removed, and a labelled ligand bound to the membrane preparation was trapped on glass filter. This glass filter was dried thoroughly, thereafter, it was mixed with cocktail for liquid scintillation, and radioactivity was measured using liquid scintillation counter. The concentration to inhibit specific binding of [^{3}H]AVP with respect to membrane preparation of test drug agent by 50% (IC50 value) was determined from regression analysis of displacement curve of test drug agent. The inhibition constant (Ki value) was determined from $Ki = IC50 / (1+[L] / Kd)$ (wherein, [L] is concentration of [^{3}H]AVP, Kd is a value determined from saturation binding test using Scatchard plot analysis). A negative logarithm of Ki value calculated from above-mentioned was calculated and pKi was determined.

As a result, example compounds of this invention showed good affinity with respect to human V_{1A} receptor with range of pKi value of 6.0-9.1.

(2) V_{1A} receptor binding test using rat liver membrane preparation

The production of rat liver membrane preparation was performed in accordance with process of Nakamura et al. (J. Biol. Chem. 258 [1983], 9283-9289). [^{3}H]AVP (0.5 nM) and rat liver membrane preparation were mixed with test drug agent of various concentration, and incubated. The assay was carried out with assay buffer of 50 mM Tris-hydrochloric acid buffer (pH = 7.4) including 10 mM magnesium chloride and 0.1 % bovine serum albumin with whole quantity 250 µl, with the incubation time of one hour at 25°C. On completion of the incubation, filtration under reduced pressure was carried out using cell harvester, the sample was passed through a glass filter (GF/B), thereby free ligand and excess buffer were removed, and a labelled ligand bound to the membrane preparation was trapped on glass filter. This glass filter was dried thoroughly, thereafter, it was mixed with cocktail for liquid scintillation, and radioactivity was measured using liquid scintillation counter. The concentration to inhibit specific binding of [^{3}H]AVP with respect to membrane preparation of test drug agent by 50% (IC50 value) was determined from regression analysis of displacement curve of test drug agent. The inhibition constant (Ki value) was determined from Ki = IC50 / (1+[L] / Kd) (wherein, [L] is concentration of [^{3}H]AVP, Kd is a value determined from saturation binding test using Scatchard plot analysis). A negative logarithm of Ki value calculated from above-mentioned was calculated and pKi was determined.

As a result, example compounds of this invention showed good affinity with respect to rat V_{1A} receptor.

(3) V_{1A} receptor antagonism in unanesthetised rat (oral administration).

Male Wistar rats were anaesthetised with pentobarbital sodium (60 mg/kg intraperitoneal administration), and polyethylene tube for sphygmomanometry was introduced to the left common carotid artery. Rats were placed in individual cages, and used for the experiment after a recovery period of one or two days. Blood pressure was measured from the artery tube via pressure transducer under unanesthetised unrestrained conditions. AVP (30 mU/kg) was administered intravenously to rats, and blood pressure increase of this time was measured. The test drug agent was suspended in 0.5 % methyl cellulose solution, it was orally-administered, and vasopressor reaction by AVP was measured. Vasopressor reaction by AVP before test drug agent administration was made 100 %, and the

inhibition ratio of vasopressor reaction by AVP after test drug agent administration was observed with time, and V_{1A} receptor antagonism was examined.

As a result, the compounds of this invention showed V_{1A} receptor antagonism activity that was potent and also continuous.

The medicinal composition containing as effective ingredient at least one compound represented by general formula (I) and (I'), pharmacologically acceptable salts thereof, hydrate or the like is prepared using carrier for the formulation, excipient, other additives usually used, formed into tablet, powder, fine granules, granules, encapsulated formulation, pill, liquid agent, injection, suppository, ointment, patch and the like and administered orally or aorally.

The clinical dose of the compounds of this invention with respect to a human is suitably determined in individual cases on consideration of symptoms, age, sex, body weight of the patient, but it is usually per adult per day orally 0.1-500 mg and this is divided into one time or several times and is administered. Because the dose changes under various kinds of conditions, there may be occasions where an amount lower than aforesaid dose range is enough.

As solid composition for oral administration in accordance with this invention, tablet, powder, granules and the like are used. In such solid composition, at least one active material is mixed with at least one inert diluent, for example lactose, mannitol, dextrose, hydroxypropylcellulose, microcrystalline cellulose, starch, polyvinylpyrrolidone, magnesium metasilicate aluminate and the like.

In accordance with normal methods, the composition may contain additives other than inert diluents, for example, a lubricant such as magnesium stearate, a disintegrating agent such as calcium carboxymethyl cellulose, a stabilising agent such as lactose, solubiliser or a solubilisation agent such as glutamic acid or aspartic acid. The tablet or pill may be coated with stomach-soluble or intestine-soluble substance such as sucrose, gelatin, hydroxypropylcellulose, hydroxypropyl methyl cellulose phthalate and the like in accordance with requirements. The liquid composition for oral administration includes pharmaceutically acceptable opacifier, solvent, suspending agent, syrup, elixir and the like, and contains a generally used inert diluent, for example purified water, ethanol. This composition may contain adjuvant such as solubilisation agent / solubiliser, wetting agent, suspending agent, and also sweetener, flavour agent, aromatic agent and preservatives besides inert diluent.

As injection agent for aoral administration, sterile aqueous or non-aqueous solution, suspension and emulsion are included. As aqueous solvent and diluent of suspending agent, for example, distilled water for injection and physiological saline are included. As non-aqueous solvent and suspending agent, for example, propylene glycol, polyethyleneglycol, vegetable oil such as olive oil, alcohol such as ethanol, detergent such as polysorbate 80 (trade name) and the like. Such composition may further contain isotonising agent, preservatives, wetting agent, emulsifier, dispersant, stabilising agent (for example lactose), solubiliser or solubilisation aid (for example glutamic acid, aspartic acid). These are sterilised for example by filtration through bacteria retaining filter, formulation of fungicide compound or irradiation. Also, these are formed into a sterile solid composition and it is dissolved in sterile water or sterile injectable solvent before use and it can be used.

The best form to be carried out invention

Hereinafter, Examples are described, and this invention is further described in greater detail. Moreover it goes without saying that this invention is not restricted only to compounds of Examples. Moreover, when the raw materials used in this invention are novel, it is described as Reference Examples.

Example 1

4-(2-methoxyphenyl)-3-(4'-biphenyl)-1,2,4-triazole (Compound Number 22).

3-(4'-biphenyl)-1,3,4-oxadiazole (538 mg) and o-anisidine (6 ml) were heated at 150°C in the absence of solvent for 12 hours. The reaction mixture was purified by silica gel column chromatography, and the title compound was obtained 95 mg (12 %) as a brown solid. The NMR data of the obtained compound are as follows.

3.63 (3H, s), 7.11 (1H, t, J = 7.5 Hz), 7.25 (1H, d, J = 8.4 Hz), 7.35-7.57 (7H, m), 7.67-7.69 (4H, m), 8.72 (1H, s).

Reference Example 1

N-(2-benzyloxyphenyl) acetamide

Acetic anhydride (20 ml) was added to ethyl acetate (100 ml) solution of 2-aminophenol (10.91 g) at room temperature and was stirred for 30 minutes. The reaction liquor was concentrated, thereafter, ethyl acetate was added to the residue, and the crystals were recovered by filtration. An acetonitrile (300 ml) liquid mixture of said crystals, benzyl bromide (18.8 g) and potassium carbonate (30.0 g) was stirred at 70°C overnight. The reaction liquor was filtered, ethyl acetate was added to the residue, it was washed with water and saturated aqueous sodium chloride solution, dried and thereafter

concentrated. The residue was purified by silica gel column chromatography, and the title compound 22.64 g (94 %) was obtained as a white solid.

Physical properties of this compound are as follows.

FAB-MS m/z: 242 (M+ + H).

1H-NMR(CDCl3) δ: 2.15 (3H, s), 5.12 (2H, s), 6.92-7.05 (3H, m), 7.35-7.48 (5H, m), 7.76 (1H, br s), 8.30-8.40 (1H, m).

Reference Example 2

N-(2-benzyloxyphenyl)-S-methyl acetothioimidate

A toluene (300 ml) liquid mixture of N-(2-benzyloxyphenyl) acetamide (22.55 g) and phosphorus pentasulfide (23.0 g) was stirred at 70°C for two hours. Supernatant fraction of the reaction liquor was separated and thereafter concentrated, the residue was purified by silica gel column chromatography, and N-(2-benzyloxyphenyl) thioacetamide 11.51 g was obtained as brown liquid. An acetonitrile (300 ml) liquid mixture of this, methyl iodide (20.0 g) and potassium carbonate (30.0 g) was stirred at 50°C for three hours. The reaction liquor was filtered, thereafter ethyl acetate was added to the residue, this was washed with water and saturated aqueous sodium chloride solution, dried and thereafter concentrated. The residue was purified by silica gel column chromatography, and the title compound 16.23 g (64 %) was obtained as red liquid. Physical properties of this compound are as follows.

FAB-MS m/z: 272 (M+ + H).

1H-NMR (CDCl3) δ: 1.97 (3H, s), 2.46 (3H, s), 4.99 (2H, s), 6.65 (1H, d, J = 10 Hz), 6.90-7.08 (3H, m), 7.28-7.49 (5H, m).

Reference Example 3

Biphenyl-4-carboxylic acid hydrazide.

An ethanol (100 ml) liquid mixture of biphenyl-4-carboxylic acid ethyl ester (2.26 g) and hydrazine monohydrate (5.0 g) was stirred at 170°C in a sealed tube container overnight. The reaction liquor was concentrated, thereafter, ethyl acetate was added, crystals were recovered by filtration, and the title compound 1.59 g (75 %) was obtained as white solid. Physical properties of this compound are as follows.

FAB-MS m/z: 213 (M+ + H).

1H-NMR (CDCl3) δ: 4.52 (2H, br s), 7.30-7.60 (3H, m), 7.60-7.90 (4H, m), 7.90-8.00 (2H, m), 9.83 (1H, br s).

Example 2

4-(2-benzyloxyphenyl)-3-(4'-biphenyl)-5-methyl-1,2,4-triazole (Compound Number 39)

A dimethylformamide (DMF, 3 ml) solution of N-(2-benzyloxyphenyl)-S-methyl acetothioimidate (300 mg) and 4-biphenylcarboxylic acid hydrazide (212 mg) was stirred at 120°C for two hours. The reaction liquor was filtered, ethyl acetate was added to the residue, this was washed with water and saturated aqueous sodium chloride solution, dried, and thereafter concentrated. The residue was purified by silica gel column chromatography, it was crystallised with hexane-ethyl acetate, and the title compound 275 mg (66 %) was obtained as white solid. The NMR data of this compound is as follows.

1H-NMR($CDCl_3$) δ: 2.31 (3H, s), 4.95 (1H, d, J = 13 Hz), 5.06 (1H, d, J = 13 Hz), 6.95-7.15 (4H, m), 7.20-7.60 (14H, m).

Example 3

2-[3-(4'-biphenyl)-5-methyl-1,2,4-triazol-4-yl] phenol (Compound Number 43).

A DMF (50 ml) liquid mixture of 4-(2-benzyloxyphenyl)-3-(4'-biphenyl)-5-methyl-1,2,4-triazole (2.78 g) and 10 % palladium-carbon (0.50 g) was stirred at room temperature overnight. The reaction liquor was filtered while hot, thereafter was concentrated, ethyl acetate was added to the residue, crystals were recovered by filtration, and the title compound (2.05 g) was obtained as grey solid. The NMR data of this compound is as follows.

1H-NMR (DMSO-d6) δ: 2.17 (3H, s), 6.95 (1H, t, J = 8 Hz), 7.07 (1H, t, J = 8 Hz), 7.30-7.53 (7H, m), 7.60-7.65 (4H, m), 10.33 (1H, s).

Reference Example 4

4-[2-(6-bromo hexyloxy) phenyl]-3-(4'-biphenyl)-5-methyl-1,2,4-triazole.

An acetonitrile (50 ml) liquid mixture of 2-[3-(4'-biphenyl)-5-methyl-1,2,4-triazol-4-yl] phenol (1.04 g), 1,6-dibromohexane (3.90 g) and potassium carbonate (3.0 g) was stirred at 50°C for 30 minutes. The reaction liquor was filtered, ethyl acetate was added to the residue, this was washed with water and saturated aqueous sodium chloride solution, dried and thereafter concentrated. The residue was purified by silica gel column chromatography, and the title compound 1.22 g (77 %) was obtained as amorphous.

Physical properties of this compound are as follows.

FAB-MS m/z: 492 (M+ + H).

1H-NMR(CDCl3) δ: 1.15-1.35 (4H, m), 1.50-1.65 (2H, m), 1.68-1.90 (2H, m), 2.29 (3H, s), 3.31 (2H, t, J = 7 Hz), 3.75-3.99 (2H, m), 7.06 (2H, t, J = 8 Hz), 7.15-7.60 (13H, m).

Example 4

4-{2-[6-(4-methylpiperazin-1-yl) hexyloxy] phenyl)-3-(4'-biphenyl)-5-methyl-1,2,4-triazole (Compound Number 54).

An acetonitrile (20 ml) liquid mixture of 4-[2-(6-bromo hexyloxy) phenyl]-3-(4'-biphenyl)-5-methyl-1,2,4-triazole (0.60 g), 1-methylpiperazine (200 mg) and potassium carbonate (2.0 g) was stirred at 70°C for two hours. The reaction liquor was filtered, chloroform-methanol (10:1) was added to the residue, this was washed with water and saturated aqueous sodium chloride solution, dried and thereafter concentrated. The residue was purified by silica gel column chromatography, it was crystallised with hexane-ethyl acetate, and the title compound 420 mg (69 %) was obtained as white solid. The NMR data of this compound is as follows.

1H-NMR($CDCl_3$) δ: 1.18-1.23 (4H, m), 1.35-1.44 (2H, m), 1.51-1.60 (2H, m), 2.22-2.30 (4H, m), 2.27 (3H, s), 2.29 (3H, s), 2.42 (6H, brs), 3.80-3.87 (1H, m), 3.91-3.98 (1H, m), 7.02-7.07 (2H, m), 7.17 (1H, dd, J = 1.7 Hz, 7.7 Hz), 7.31-7.56 (10H, m).

Example 5

4-{2-[4-(4-piperidyl) butoxy] phenyl)-3-(4'-biphenyl)-5-methyl-1,2,4-triazole (Compound Number 72).

An acetonitrile (10 ml) liquid mixture of 2-[3-(4'-biphenyl)-5-methyl-1,2,4-triazol-4-yl] phenol (440 mg), 4-[4-(1-trityl) piperidyl] butyltoluene sulphonate (890 mg) and potassium carbonate (2.0 g) was stirred at 80°C for 3 hours. The reaction liquor was filtered, the filtrate was concentrated, the residue was purified by silica gel column chromatography, and N-trityl body of the title compound 1.01 g (quant.) was obtained. From this, 500 mg were deprotected in hydrochloric acid-ethanol-ethyl acetate, and the title compound 220 mg (67 %) was obtained. The NMR data of this compound is as follows.

1H-NMR (DMSO-d6) δ: 0.90-1.75 (11H, m), 2.30 (3H, s), 2.55-2.85 (2H, m), 3.00-3.25 (2H, m), 3.80-4.05 (2H, m), 7.10-7.80 (13H, m), 8.81 (1H, br), 9.05 (1H, br).

Example 6

4-{2-[3-(3-pyridyl) propyl] phenyl)-3-(4'-biphenyl)-5-methyl-1,2,4-triazole (Compound Number 85).

A diethyl azodicarboxylate (210 mg) was added under ice cooling to a THF (5 ml) solution of 2-[3-(4'-biphenyl)-5-methyl-1,2,4-triazol-4-yl] phenol (220 mg), 3-(3-pyridyl) propanol (140 mg) and triphenyl phosphine (310 mg), and the mixture was stirred for 20 minutes. The reaction liquor was

concentrated, thereafter, the residue was purified by silica gel column chromatography, crystallised from hexane-ethyl acetate, and the title compound 156 mg (52 %) was obtained as white solid. The NMR data of this compound is as follows.

1H-NMR($CDCl_3$) δ: 1.75-1.95 (2H, m), 2.32 (3H, s), 2.30-2.60 (2H m), 3.75-4.00 (2H, m), 6.95-7.60 (15H, m), 8.30 (1H, s), 8.39 (1H, d, J = 5 Hz).

Example 7

4-(2-{2-[4-(4-methylpiperazin-1-yl) carbonyl phenyl] ethynyl) phenyl)-3-(4'-biphenyl)-5-methyl-1,2,4-triazole (Compound Number 41)

A liquid mixture of 4-(2-iodophenyl)-3-(4'-biphenyl)-5-methyl-1,2,4-triazole (1.30 g), triethylamine (10 ml), pyridine (4 ml), copper iodide (56 mg), palladium dichloro bis (triphenyl phosphine) (104 mg) and triphenyl phosphine (780 mg) was stirred at 70°C overnight. After filtration, the reaction liquor was concentrated, the residue was purified by silica gel column chromatography, it was crystallised with hexane-ethyl acetate, and the title compound 1.22 g (68 %) was obtained as beige powder. The NMR data of this compound is as follows.

1H-NMR (DMSO-d6) δ: 2.25-2.47 (4H, m), 2.33 (3H, s), 2.38 (3H, s), 3.42 (2H, brs), 3.79 (2H, brs), 7.30-7.58 (17H, m).

Example 8

4-(2-{2-[4-(4-methylpiperazin-1-yl) carbonyl phenyl] ethyl) phenyl)-3-(4'-biphenyl)-5-methyl-1,2,4-triazole (Compound Number 42).

4-(2-{2-[4-(4-methylpiperazin-1-yl) carbonyl phenyl] ethynyl) phenyl)-3-(4'-biphenyl)-5-methyl-1,2,4-triazole (1.09 g) was subjected to catalytic reduction in methanol (30 ml) using 10 % palladium-carbon (700 mg) as catalyst for three days. The reaction liquor was filtered, thereafter, the residue was purified by silica gel column chromatography, it was crystallised with hexane-ethyl acetate, and the title compound 1750 mg (67 %) was obtained as white powder. The NMR data of this compound is as follows.

1H-NMR (DMSO-d6) δ: 2.20-2.65 (8H, m), 2.23 (3H, s), 2.30 (3H, s), 3.41 (2H, brs), 3.75 (2H, brs), 6.93 (2H, d, J = 7.8 Hz), 7.17-7.56 (15H, m).

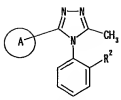
Moreover, the structural formulae of representative compounds of novel triazole compounds of this invention including compounds obtained in aforesaid Examples are shown in following Tables 1-8 together with the physical properties thereof. Moreover, the NMR data thereof are also shown with the physical properties in Tables 9-11 mainly for compounds described as amorphous crystal among the

compounds other than compounds described in Examples. Moreover, the compounds other than the compounds described in Examples can be readily produced in more or less the same way as aforesaid production methods and the methods described in Examples or by application of slight modifications self-evident to a person skilled in the art to these.

Moreover notations in the Tables have following meanings.
No: compound number,
NMR: nuclear magnetic resonance spectrum,
m.p.: melting point, Amorph.: amorphous crystal,
Me: methyl, Et: ethyl, Pr: propyl,
iPr: isopropyl, Bn: benzyl,

Moreover, "4-", "5-" and "6-" attached to the substituent in the Tables means that the substituent is bonded to "4", "5" or "6" position of the structural formula in the Table and is not concerned with chemical name.

Table 1



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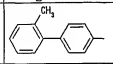
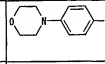
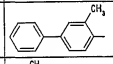
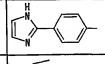
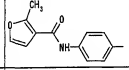
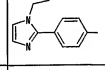
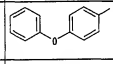
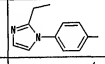
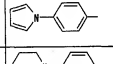
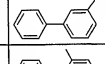
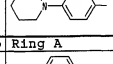
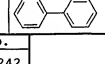
1		-OMe	161-163	15		-OMe	190-192
2		-OMe	170-172	16		-OBn	185-187
6		-OEt	204-206	19		-OBn	196-198
10		-OMe	149-150	20		-OBn	Amorph.
13		-OMe	181-183	94		-OMe	112-113
14		-OMe	125-126	95		-OMe	142-143

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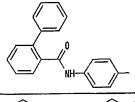
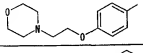
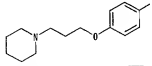
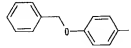
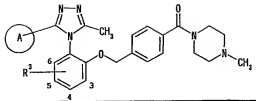
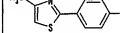
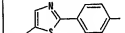
7		-OMe	241-242
11		-OMe	157-159
12		-OMe	Amorph.
93		-OMe	157-158

Table 2



No	Ring A	R^3	m.p.	No	Ring A	R^3	m.p.
3		H	Amorph.	17		6-Me	Amorph.
4		H	Amorph.	18		6-Me	Amorph.
5		H	Amorph.	21		6-Me	Amorph.

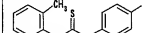
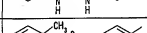
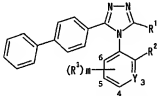
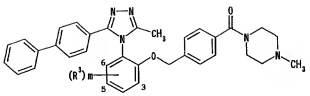
No	Ring A	R^3	m.p.
8		H	Amorph.
9		H	Amorph.

Table 3



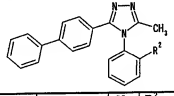
No	R^1	R^2	R^3	Y	m.p.	No	R^1	R^2	R^3	Y	m.p.
22	H	-OMe	H	CH	205-207	37	Me	-Ph	H	CH	190-191
23	Et	-OMe	H	CH	122-123	38	Me	-iPr	H	CH	164-165
24	Pr	-OMe	H	CH	145-146	39	Me	-OBn	H	CH	171-172
33	Me	-OMe	H	CH	183-184	40	Me	-I	H	CH	203-205
34	Me	-OEt	H	CH	153-155	43	Me	-OH	H	CH	>300
35	Me	-OPr	H	CH	111-112	44	Me	-OH	6-Me	CH	263-265
36	Me	-Me	4-Me, 6-Me	CH	125-127	97	Me	-OMe	H	N	183-184

Table 4



No	R^3	m.p.	No	R^3	m.p.
25	5-SO_2-Et	117-119	30	5-CN	167-169
26	5-Me	181-183	31	5-CF_3	117-120
27	5-OMe	89-91	32	5-NO_2	136-138
28	5-Cl	100-102	79	6-Me	161-164
29	5-NH_2	215-218	81	H	179-180

Table 5



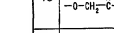
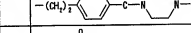
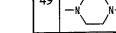
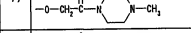
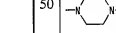
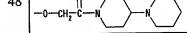
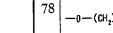
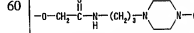
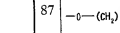
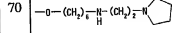
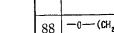
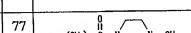
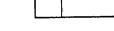
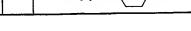
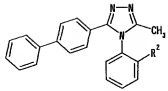
No	R^2	m.p.	No	R^2	m.p.
45		134-136	41		128-130
46		154-164	42		92-95
49		204-206	47		178-180
50		98-99	48		Amorph.
78		Amorph.	60		Amorph.
87		Amorph.	70		73-73
88		Oil	77		Amorph.

Table 6



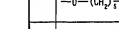
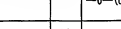
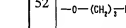
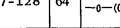
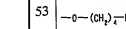
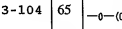
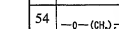
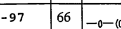
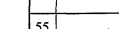
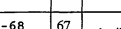
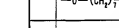
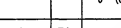
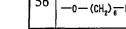
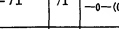
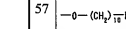
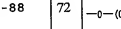
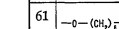
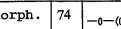
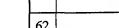
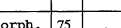
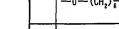
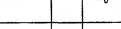
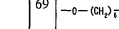
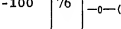
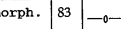
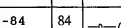
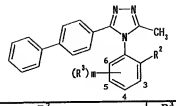
No	R^2	m.p.	No	R^2	m.p.
51		115-116	63		137-139
52		127-128	64		80-82
53		103-104	65		107-108
54		96-97	66		104-105
55		67-68	67		79-81
56		70-71	71		Amorph.
57		87-88	72		Amorph.
61		Amorph.	74		120-122
62		Amorph.	75		Amorph.
69		98-100	76		Amorph.
73		Amorph.	83		204-205
82		82-84	84		180-182
			85		140-141
			86		80-82

Table 7



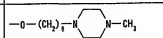
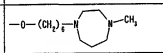
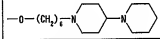
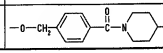
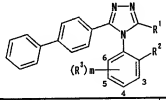
No	R^2	R^3	m.p.
58		6-Me	Amorph.
59		6-Me	Amorph.
68		6-Me	90-91
80		6-Me	147-150

Table 8



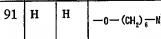
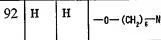
No	R^1	R^2	R^3	m.p.
89	Me	H	4-OH	290-292
90	Me	H	3-OH	277-279
91	H	H		124-125
92	H	H		85-87
96	Me			148-150

Table 9

Compound	^{1}H−NMR δ (ppm)
3	2.14(3H, s), 2.31(3H, s), 2.46(2H, br s), 3.42(2H, br s), 3.79(2H, br s), 4.93-5.06(2H, m), 7.00-7.05(3H, m), 7.10(1H, dt, J=7.8, 1.0 Hz), 7.21(1H, dd, J=7.8, 1.9Hz), 7.31(3H, t, J=8.8Hz), 7.39(2H, dd, J=6.9, 1.9Hz), 7.48(1H, m)/$CDCl_3$
4	2.33(6H, s), 2.49(2H, br s), 3.41(2H, br s), 3.79(2H, br s), 4.93-5.06(2H, m), 7.06(2H, d, J=8.3Hz), 7.11-7.17(2H, m), 7.23(1H, m), 7.32(2H, d, J=10.3Hz), 7.52(1H, m), 7.60-7.63(2H, m), 8.11(2H, d, J=9.3Hz)/$CDCl_3$
5	2.27(3H, s), 2.32(3H, s), 2.47(2H, br s), 3.41(2H, br s), 3.79(4H, br s), 4.94-5.06(2H, m), 6.50-6.52(2H, m), 7.00-7.07(4H, m), 7.18-7.21(3H, m), 7.31(2H, d, J=8.3Hz), 7.43(1H, m)/$CDCl_3$
8	1.66(3H, s), 2.25(3H, s), 2.32(3H, s), 2.45(2H, br s), 3.39(2H, br s), 3.75(2H, br s), 4.93-5.03(2H, m), 7.00-7.19(4H, m), 7.22(1H, m), 7.26-7.37(7H, m), 7.48(1H, m), 7.81(1H, br s), 7.91(1H, br s)/$CDCl_3$
9	1.64(3H, s), 2.23(3H, s), 2.28(3H, s), 2.32(2H, br s), 2.44(2H, br s), 3.37(1H, br s), 3.77(1H, br s), 4.90-4.98(2H, m), 7.00-7.09(5H, m), 7.11-7.25(9H, m), 7.26(1H, m), 7.43(1H, m), 7.56(1H, br s), 7.71(1H, d, J=7.6Hz), 8.62(1H, br s)/$CDCl_3$
12 fumarate	1.30-1.70(6H, m), 1.90-2.05(2H, m), 2.12(3H, s), 2.40-2.80(6H, m), 3.70(3H, s), 8.90-4.05(2H, m), 6.54(2H, s), 6.75-7.55(8H, m)/DMSO-d_6
17	1.95(3H, s), 2.26(3H, s), 2.31(3H, s), 2.48(3H, s), 3.38(2H, br s), 3.76(2H, br s), 5.03(2H, m), 6.89(1H, d, J=0.9Hz), 6.92-7.00(2H, m), 7.10(2H, d, J=6.9Hz), 7.26-7.44(3H, m), 7.51(2H, m), 7.82(2H, dd, J=6.9, 2.0Hz)/$CDCl_3$
18	1.95(3H, s), 2.26(3H, s), 2.31(3H, s), 2.45(2H, br s), 2.74(3H, s), 3.38(2H, br s), 3.76(2H, br s), 4.98-5.08(2H, m), 6.91-7.00(2H, m), 7.04(2H, d, J=8.3Hz), 7.28-7.37(4H, m), 7.48(2H, dd, J=6.9, 1.9Hz), 7.77(2H, dd, J=6.9, 1.9Hz)/$CDCl_3$

Table 10

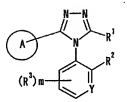
Compound	^{1}H−NMR δ (ppm)
20	1.22(3H, t, J=7.4Hz), 2.31(3H, s), 2.62(2H, q, J=7.8Hz), 4.97-5.10 (2H, m), 6.96(1H, d, J=0.9Hz), 7.00-7.29(8H, m), 7.33-7.38(3H, m), 7.47-7.55(3H, m)/CDCl$_3$
21	2.05(3H, s), 2.27(3H, s), 2.32(3H, s), 2.43(2H, br s), 3.36(2H, br s), 3.75(2H, br s), 5.05(2H, m), 6.80(1H, d, J=3.9Hz), 6.88(1H, d, J=7.9Hz), 7.03(1H, d, J=7.9Hz), 7.08-7.11(3H, m), 7.26-7.44(6H, m), 7.50-7.53(2H, m)/CDCl$_3$
48 fumarate	1.25-1.90(10H, m), 2.24(3H, s), 2.45-3.00(5H, m), 3.65-3.80(2H, m), 4.30-4.40(2H, m), 4.92(1H, d, J =15Hz), 5.04(1H, d, J=15Hz), 6.56 (2H, s), 7.00-7.70(13H, m)/DMSO-d$_6$
51	1.01-1.12(2H, m), 1.16-1.29(2H, m), 1.37-1.48 (2H, m), 2.04-2.21 (10H, m), 2.10(3H, s), 2.16(3H, s), 3.81-4.01(2H, m), 7.12(1H, t, J=7.7Hz), 7.27(1H, d, J=8.1Hz), 7.34-7.56(7H, m), 7.63-7.67(4H, m)
55	1.20(6H, brs), 1.36-1.44(2H, m), 1.50-1.57(2H, m), 2.24-2.30(4H, m), 2.28 (3H, s), 2.29(3H, s), 2.43(6H, brs), 3.80-3.87(1H, m), 3.90-3.98(1H, m), 7.02-7.06(2H, m), 7.16(1H, dd, J=1.8Hz, 8.1Hz), 7.31-7.56(10H, m)/CDCl$_3$
58	1.15-1.20(6H, m), 1.47-1.67(4H, m), 1.91-2.00(2H, m), 1.99(3H, s), 2.25(3H, s), 2.83(3H, s), 3.03(1H, brs), 3.40-3.70(4H, m), 3.98-4.07(3H, m), 7.06(1H, d, J=7.8Hz), 7.19(1H, d, J=8.7Hz), 7.37-7.54 (6H, m), 7.69-7.75(4H, m)/DMSO
59	1.13-1.18(4H, m), 1.51-1.60(4H, m), 1.96(3H, s), 2.14(2H, brs), 2.26(3H, s), 2.77(3H, s), 2.98(2H, brs), 3.18-3.77(8H, m), 7.06(1H, d, J=7.5Hz), 7.18(1H, d, J=8.4Hz), 7.36-7.53(13H, m), 11.40-11.55 (1H, m), 11.66-11.84(1H, m)/DMSO
60	1.53(2H, quint, J=7.0Hz), 2.19(2H, t, J=7.0Hz), 2.24-2.42(8H, m), 2.25(3H, s), 2.33(3H, s), 3.12(2H, quart, J=7.0Hz), 4.25(1H, d, J=14.6Hz), 4.37(1H, d, J=14.6Hz), 5.80(1H, t , J=7.0Hz), 6.99(1H, brd, J=8.4Hz), 7.23(1H, brd, J=7.8Hz), 7.321-7.58(11H, m)/CDCl$_3$

Table 11

Compound	^{1}H−NMR δ (ppm)
6 1 3HCl	0.90-1.20(6H, m), 1.25-1.70(2H, m), 2.40(3H, s), 2.75-3.00(4H, m), 3.20-3.55(4H, m), 3.80-4.05(2H, m), 4.50-4.65(2H, m), 6.70-6.80 (1H, m), 7.10-7.80(13H, m), 8.80-8.45(2H, m), 11.41(1H, br)/ DMSO-d_6
6 2 3HCl	0.90-1.20(6H, m), 1.25-1.70(2H, m), 2.36(3H, s), 2.80-3.20(4H, m), 3.40-3.75(4H, m), 3.80-4.05(2H, m), 4.35-4.55(2H, m), 6.69-8.15 (17H, m)/DMSO-d_6
6 8	1.16-1.22(4H, m), 1.36-1.46(4H, m), 1.52-1.60(8H, m), 1.71-1.85 (4H, m), 2.16-2.21(3H, m), 2.29(3H, m), 2.48(4H, brt, J=5.3Hz), 2.85-2.95(2H, m), 3.80-3.87(1H, m), 3.91-3.98(1H, m), 7.02-7.06 (2H, m), 7.16(1H, dd, J=1.7Hz, 8.0Hz), 7.31-7.56(10H, m)/$CDCl_3$
7 1 2HCl	0.90-1.75(9H, m), 2.30(3H, s), 2.50-2.75(2H, m), 3.00-3.15(2H, m), 3.80-4.05(2H, m), 7.10-7.80(13H, m), 8.79(1H, br), 9.02(1H, br)/ DMSO-d_6
8 2	2.28-2.46(4H, m), 2.29(3H, s), 2.31(3H, s), 3.35(2H, brs), 3.75(2H, brs), 4.95(1H, d, J=12.0Hz), 5.05(1H, d, J=12.0Hz), 7.01(1H, d, J=6.6Hz), 7.10(2H, t, J=9.0Hz), 7.22-7.58(14H, m)/$CDCl_3$
8 3	2.34(3H, s), 4.91(1H, d, J=14 Hz), 5.05(1H, d, J=14Hz), 6.84(1H, d, J=5Hz), 6.96(1H, d, J=8Hz), 7.10-7.60(14H, m), 8.45(1H, t, J=5Hz)/ $CDCl_3$
8 4	1.70-1.90(2H, m), 2.32(3H, s), 2.34-2.52(2H, m), 3.70-3.95(2H, m), 6.87(1H, d, J=5Hz), 6.98(1H, d, J=8Hz), 7.11(1H, t, J=7Hz), 7.30-7.60(14H, m), 8.38(1H, t, J=5Hz)/$CDCl_3$
8 5	1.75-1.95(2H, m), 2.32(3H, s), 2.30-2.60(2H, m), 3.75-4.00(2H, m), 6.95-7.60(15H, m), 8.30(1H, s), 8.39(1H, d, J=5Hz)/$CDCl_3$
8 7 2HCl	1.05-1.70(8H, m), 2.35(3H, s), 3.85-4.05(2H, m), 6.95-7.75(17H, m) /DMSO-d_6
8 8	1.10(8H, m), 2.30(3H, s), 3.54(2H, t, J=6Hz), 3.80-4.00(2H, m), 7.00-7.60(13H, m)/$CDCl_3$

Patent Claims.

1. A medicinal composition characterised by containing a triazole derivative represented by following general formula (I) or a pharmacologically acceptable salt thereof and a pharmacologically acceptable carrier.



(I)

(wherein, the symbols in the formula have the following definitions,

A ring:

a) a benzene ring which may be substituted by 1-3 substituents selected from halogen, nitro, amino, lower alkyl group or a group represented by -X-R4 or,

b) a thiophene ring which may be substituted by aryl group,

R1: hydrogen atom or lower alkyl group,

R2: hydrogen atom, halogen atom, hydroxyl group, optionally substituted alkoxy group, optionally substituted lower alkyl group, optionally substituted lower alkynyl group or optionally substituted amino group,

R3: hydrogen atom, halogen atom, amino, nitro, cyano, trifluoromethyl, lower alkyl, -O-lower alkyl group, or

it may link with R2 group to form a cycloalkyl ring,

Y: CH or N,

X: single bond, -NH-CO-, -CO-NH-, -NH-CO-NH-, -NH-CS-NH-, -(CH2)k-O- or -O-(CH2)k- group,

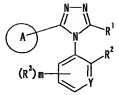
R4: an aryl group which may be substituted by lower alkyl or aryl group; a 5-6 membered heteroaryl group which may be substituted by lower alkyl group; or a 3-8 membered saturated heterocyclic group which may be substituted by lower alkyl group,

m: an integer of 1-3,

k: an integer of 0-5).

2. A medicinal composition in accordance with Claim 1 which is a vasopressin V_{1A} receptor antagonist.

3. A triazole derivative represented by following general formula (I')



(I')

(wherein, the symbols in the formula have the following definitions,

A ring:

a) a benzene ring which may be substituted by 1-3 substituents selected from halogen, nitro, amino, lower alkyl group or a group represented by -X-R4 or,

b) a thiophene ring which may be substituted by aryl group,

R1: hydrogen atom or lower alkyl group,

R2: hydrogen atom, halogen atom, hydroxyl group, optionally substituted alkoxy group, optionally substituted lower alkyl group, optionally substituted lower alkynyl group or optionally substituted amino group,

R3: hydrogen atom, halogen atom, amino, nitro, cyano, trifluoromethyl, lower alkyl, -O-lower alkyl group, or

it may link with R2 group to form a cycloalkyl ring,

Y: CH or N,

X: single bond, -NH-CO-, -CO-NH-, -NH-CO-NH-, -NH-CS-NH-, -(CH2)k-O- or -O-(CH2)k- group,

R4: an aryl group which may be substituted by lower alkyl or aryl group; a 5-6 membered heteroaryl group which may be substituted by lower alkyl group; a 3-8 membered saturated heterocyclic group which may be substituted by lower alkyl group,

m: an integer of 1-3,

k: an integer of 0-5,

Wherein, the compound wherein A ring is biphenyl group, R1 group is methyl group, Y is CH, m is 1, R3 group is hydrogen atom, and also R2 group is methoxy group is excluded),

or a pharmacologically acceptable salt thereof.

4. A triazole derivative in accordance with Claim 3, wherein

R2 group is

1) an alkoxy, lower alkyl or lower alkynyl group having substituent selected from the group represented by formula -R5, -O-(CH2)p-R5, -NH-(CH2)p-R5, -CO-(CH2)p-R5, -CO-O-(CH2)p-R5 and -CO-NH-(CH2)p-R5;

[wherein, R5 is i) hydrogen atom, or ii) aryl, a 5-6 membered heteroaryl or a 3-8 membered saturated heterocyclic group (these ring groups may be further substituted by halogen atom, amino, nitro, cyano, lower alkyl, -O-lower alkyl, -COO-lower alkyl, -CO-3-8 membered saturated heterocycle, -CO-3-8 membered saturated heterocycle-3-8 membered saturated heterocycle, -CO-3-8 membered saturated heterocycle-lower alkyl, aryl, a 5-6 membered heteroaryl or a 3-8 membered saturated heterocyclic group which may be substituted by lower alkyl group), and p is an integer of 0-4]; or

2) a group represented by

(wherein X is CH-R6, N-R6, O or S, R6 is lower alkyl, -O-lower alkyl, -COO-lower alkyl, -CO-3-8 membered saturated heterocycle-lower alkyl, aryl, a 5-6 membered heteroaryl or a 3-8 membered saturated heterocyclic group, and q and r are integers of 1-3);
or a pharmacologically acceptable salt thereof.

5. A triazole derivative in accordance with Claim 4, wherein
A ring is a group represented by formula

(wherein, X and R4 are as described before, and R7 is hydrogen atom, halogen atom, nitro, amino or lower alkyl group),
or a pharmacologically acceptable salt thereof.

6. A triazole derivative in accordance with Claim 5, wherein Y is CH and R2 group is a group selected from the group represented by following formula or a pharmacologically acceptable salt thereof.

-O-(CH2)n-R5
-O-(CH2)n-O-(CH2)p-R5
-O-(CH2)n-NH-(CH2)p-R5
-O-(CH2)n-CO-(CH2)p-R5
-O-(CH2)n-CO-O-(CH2)p-R5
-O-(CH2)n-CO-NH-(CH2)p-R5
(wherein, R5 and p are described as above, and n is an integer of 1-12).

7. A triazole derivative in accordance with Claim 6, wherein the A ring is 4-biphenyl ring, R1 is methyl group and R2 is a group represented by -O-(CH2)n-R5, or a pharmacologically acceptable salt thereof.

8. 4-(2-benzyloxyphenyl)-3-(4'-biphenyl)-5-methyl-1,2,4-triazole,
4-{2-[5-(4-methylpiperazin-1-yl) pentyloxy] phenyl}-3-(4'-biphenyl)-5-methyl-1,2,4-triazole,
4-{2-[6-(4-methylpiperazin-1-yl) hexyloxy] phenyl}-3-(4'-biphenyl)-5-methyl-1,2,4-triazole,
4-{2-[7-(4-methylpiperazin-1-yl) heptyloxy] phenyl}-3-(4'-biphenyl)-5-methyl-1,2,4-triazole,
4-{2-[8-(4-methylpiperazin-1-yl) octyloxy] phenyl}-3-(4'-biphenyl)-5-methyl-1,2,4-triazole,
4-{2-[6-(4-methylpiperazin-1-yl) hexyloxy]-6-methylphenyl}-3-(4'-biphenyl)-5-methyl-1,2,4-triazole,
4-{2-[6-(4-methyl homopiperazin-1-yl) hexyloxy]-6-methylphenyl}-3(4'-biphenyl)-5-methyl-1,2,4-triazole,
4-[2-(6-piperidino hexyloxy) phenyl]-3-(4'-biphenyl)-5-methyl-1,2,4-triazole,
4-{2-[6-(4-piperidino piperidin-1-yl) hexyloxy] phenyl}-3-(4'-biphenyl)-5-methyl-1,2,4-triazole,
4-{2-[6-(4-piperidino piperidin-1-yl) hexyloxy]-6-methylphenyl}-3-(4'-biphenyl)-5-methyl-1,2,4-triazole,
4-{2-[4-(4-piperidyl) butoxy] phenyl}-3-(4'-biphenyl)-5-methyl-1,2,4-triazole,
4-{2-[4-(4-methylpiperazin-1-yl) carbonyl phenyl] methoxy-6-methylphenyl}-3-(4'-biphenyl)-5-methyl-1,2,4-triazole,
4-{2-[4-(4-piperidino piperidin-1-yl) carbonyl phenyl] methoxy-6-methylphenyl}-3-(4'-biphenyl)-5-methyl-1,2,4-triazole,
4-{2-[4-(4-methylpiperazin-1-yl) carbonyl phenyl] methoxyphenyl}-3-(4'-biphenyl)-5-methyl-1,2,4-triazole,
4-{2-[3-(3-pyridyl) propyl] phenyl}-3-(4'-biphenyl)-5-methyl-1,2,4-triazole, or a pharmacologically acceptable salt thereof

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